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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/787,284	02/26/2004	Paul M. Skonezny	GY0111 (NP)	5398

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EXAMINER	
WALICKA, MALGORZATA A	

ART UNIT	PAPER NUMBER
1652	

NOTIFICATION DATE	DELIVERY MODE
10/18/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/787,284	SKONEZNY ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 8-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 8-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

The response filed August 9, 2007 comprising applicants' REMARKS regarding the last Office Action mailed to applicants May 9, 2007, is acknowledged. The claims or specification have not been amended. Pending claims 1-6, and 8-26 are under examination.

DETAILED ACTION

Priority

The applicants claim of benefits of the US provisional application 60/451,842, filed 03/04/03, has been noted. Priority of the examined claims to the provisional application has been granted.

Rejection under 35 USC 112, second paragraph

Claims 1-6, 8-21, 22-24 and 25-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1, 2, 14, 18, 22 and 25 are rejected for reasons stated in the last Office action. The reasons are repeated herein for the applicants' convenience.

The claims are confusing in limitations "at least about 1%", "about 2% to about 10%", about "4% to about 15%" and about "5% to about 8%".

The limitation "at least about" is confusing, because "at least" sets the minimum of a range, and "about" refers to both, the lower and upper limits of the range. For examination purposes the examiner assumes that the ddA solution is at least 1%.

Claims 19 and 20 are confusing as depending on claim 10. It seems that the claims should depend on claim 1.

Response to Applicants argument

1. Applicants position, REMARKS, page 6/8, third paragraph, is, "The term 'about' is commonly used in the English language and is defined as 'near in time, number, degree etc.; approximately', e.g. Its about five miles form here."

Applicants' argument has been fully considered but is found not persuasive for the following reasons.

Firstly, the claims do not use the limitation "about", but "at least about" or "from about 2% to about 10%" etc. About 2% is definite. At least 2% is definite. However, at least about 2% is not. The limitation at least requires that the value cannot be smaller than 2%. But the limitation about requires that the value is lower or higher than 2%. Both limitation exclude each other. A value cannot be 2% and at the same time less than 2%. The incorrectness of the limitation "at least about" has nothing to do with the usage of the term "about in the English language.

Secondly the limitation from 2% to 10% sets the lower limit 2% and the upper limit 10%. The limitation from about 2% to about 10% does not set the lower and upper limit as long as applicants do not **define what "about" means**. There is no definition of about in the disclosure. Is about 1%, 2% or something else? If it is 1% the limits of the ranges are 1%-10%; 1%-9%; 1%-11%, 2%-10%; 2%-9%; 2%- 11%, 3%-9%, 3-10%, 3%-11%. If about is 2% the limits are 0% - 8%, 0%-10%, 0% -12, 2% - 8%, 2%-10%,

2% -12, and 4% - 8%, 4%-10%, 4% -12%. Although the limits quoted here are presented by discrete values, there is a continuum of the limitations wherein the lower limit is from 0%-4% and the upper from 8%-12%. To give an example closer to the everyday life, let's take the sentence "It is from about 20 miles to about 100 miles from here." Is a driver asking for the distance given an informative answer?

2. Applicants submit there are thousands of issued patents the claims of which contain the limitation "at least about", and that applicants expect consistency in the application of US laws.

Although this is true, the examiner is not in position to comment on the issued patents or on consistency of the Office in the application of the US laws.

For the reasons explained in the previous action and above the rejection of claims 1-6, 8-21, 22-24 and 25-26 are maintained.

Rejection under 35 USC 103

Claims 1-6, 8-18, 20 and 22-26 are rejected over Farina et al., US Patent 5,011,774 published Oct. 1991, in view of Daddona et al., published Oct. 1884 and common knowledge in the art as exemplified by Dessouki et al., published 2002. The reasons for rejection were explained in the last Office Action and are repeated here for applicants' convenience.

Farina et al. teach production of ddI from ddA using adenine deaminase wherein the enzyme is immobilized; see column 6, line 1-23, and claim 3. They particularly teach using Eupergit to which the adenine deaminase may be bound using conventional

techniques. Eupergit beads have diameter of 250 microns; see Boller et al, page 509, the upper part of the right column; included in examiner's references. The concentration of ddA in solution of Farina et al. is 2.4% to 4.8%, which is more than 1%, and certainly about 4% and about 5%; see column 8, lines 61-68. Farina et al. also teach retaining a reaction mother liquor after the isolation step and repeating the contacting step at least once as required by claim 20 of the instant application; see column 9, line 7.

Farina et al. do not teach, however, human adenosine deaminase. Daddona et al. teach human adenosine deaminase of the same sequence as that used in the instant application; see sequence alignment enclosed.

It would have been obvious for one having skills in the art, who would like to produce the anti-HIV drug ddI, to use teachings of Farina et al. and replace calf enzyme of Farina by human adenosine deaminase taught by Daddona. The human enzyme, as long as it is set for by SEQ ID NO: 1, may be coded by DNA molecules having any modification from the natural cDNA as long as the modification is within the degeneracy of genetic code. Limitation in claims 9 and 24 "or SEQ ID NO: 3" does not change the product used in the method. The method of obtaining the enzyme, i.e. from a transformed organism, particularly form E. coli does, not further limit the enzyme because it is still the same enzyme. Claims 10-12 are "product by process claims" and as such do not further limit the product used in the method.

The motivation is provided by Farina et al: "Although adenosine deaminase (ADA) from calf spleen was used in the actual examples, it is believed that any

preparation of adenosine aminohydrolase (or 'deaminase,' EC 3.5.4.4.) would be suitable", column 6, line 8. Human adenine deaminase disclosed by applicants is a preparation of an adenosine aminohydrolase, or 'deaminase', and is classified as EC 3.5.4.4.

The expectation of success is very high because of successful production of ddI demonstrated by Farina. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made, and was as a whole, *prima facie* obvious.

Claims 5, 6, 12 and 13 are rejected as obvious because their limitations "support is functionalized" and "attachment of the enzyme to the insoluble support is achieved using an activating agent" belong to "conventional technique" quoted by Farina, and consist common knowledge in the art as exemplified by Dessouki et al., page 433.

Claims 3 and 15 are included in this rejection because the limitation of pH to 7.5-9 is related to the enzymatic reaction which is nucleophilic in nature, therefore the alkaline pH favors this reaction. This is common knowledge of those skilled in the art, as exemplified on page 43, **Results and Discussion** (i) **Effect of Incubation pH,** in Dessouki. It is also common knowledge of those in the art that the immobilized enzyme retains 90%-85% of its activity at the alkaline pH of 8-9 (Fig. 5 of Dessouki). Thus, the recited pH range ensures the efficient reaction. Furthermore, it is a routine way to use a column packed with immobilized enzyme as claim 16 requires, because that makes the quantitative washing out of products, as well as preparing the immobilized enzyme for the subsequent use, much easier. Claim 14 reciting limitation "the insoluble support is at least about 40 U/g is rejected, as dependent on claim 1, over Farina and Daddona,

and further in view of Dessouki. Dessouki teaches that the maximum amount of enzyme immobilized on different polymeric support is 42 units/g. Since one who is skilled in the art would like to produce ddI, a HIV drug, efficiently, it would have been obvious for him to use at least 40 U/g following Dessouki's teachings.

Response to Applicants argument

In their argument presented on page 7/8, second paragraph of the REMARKS, applicants argue that the above 103 rejection is a hindsight reconstruction of the invention from the various references, which is improper. The applicant also urge the examiner

> "to consider the cited references as of the time of filling Applicants invention, i.e., February 26, 2004, without prior knowledge of the claimed invention. In an objective analysis, where would the references lead one of ordinary skill in the art?"

Applicants' position has been fully considered but is found not persuasive.

Firstly, the instant application's effective filing date its that of its provisional application 60/451,842 i.e., March 4, 2003.

Secondly, it is the very essence of the obviousness rejection that it is built on the information from various references.

Thirdly, synthesis of ddI, chemical, enzymatic, by microorganisms and by engineered microorganisms, has been known for half a century as have been the

methods of ddI purification. Many chemical companies had been synthesized and purified ddI for many years before the invention. The development in ddI production and purification has been accelerated since late 1980, when the compound was introduced to HIV therapy. The dates of the basic documents used in the 103 rejection are **1991** (Farina et al.) and **1984** (Daddona et al.). Perusal of applicants own IDS provides evidence that that dates of information necessary for making the invention are rather old.

Fourthly, Applicants do not present any concrete proof that the above 103 rejection is a hindsight reconstruction, nor they objectively analyze where would the references lead one of ordinary skill in the art. Thus, the question "In an objective analysis, where would the references lead one of ordinary skill in the art" remains rhetorical.

In conclusion, claims 1-6, 8-18, 20 and 22 - 26 remain rejected.

103 rejection of claims 19 and 21

Claims 19 and 21 depending on claim 1 are rejected over Farina et al., US Patent 5,011,774 published Oct. 1991 (quoted in IDS) encld, in view of Daddona et al., published Oct. 1884 (quoted in IDS) and common knowledge in the art as exemplified by Dessouki et al., published 2002 (quoted in IDS) and Beach et al (*Strategy for Industrial Scale Production of Dideoxyinosine: Enzymatic Deamination of Dideoxyadenosine by Adenosine Deaminase,* Nucleosides and Nucleotides, 1991, 10/7, 1499-1505, included in IDS).

Claim 19 is directed to the method of claim 1 wherein the ddI isolation step includes sequentially distilling the ddI solution and adding water until a ddI slurry in aqueous mother liquor is obained and the pH is less then about 8.

Beach et al teach performing reaction of adenosine deaminase with ddA in water, and diluting the product 1: 25 in water; see page 1503 description of Fig. 1. It would, therefore, have been obvious for one having ordinary skills in the art at the time of invention to use water as the solvent for reaction of adenine deaminase with ddI, and that is what applicants did. The reaction of adenine deaminase with ddA is in the instant invention performed in water at pH from 7 to 9.5 (see claims 15 –18). Therefore, the pH less than 8 is obvious when the ddI is further diluted in water that itself has pH 7.4. As to obtaining a slurry in water, for the reasons of convenience one having skills in the art would distill ddI in water, i.e. without changing the solvent, instead, for example, crystallizing ddI from methanol.

All together the invention of claim 19 was within the ordinary skill in the art to make and use at the time it was made, and was as a whole, *prima facie* obvious.

Claim 21 is directed to the claimed method of production of ddI by adenosine deaminase from ddA, wherein the isolating step produces a yield at least 96% ddI that is about 99% pure.

Beach et al teach that under conditions used by applicants (40 U/g of the enzyme, claim 14) and 4-15% (0.2M- 0.67M) of ddA in water (claims 17-18) the conversion of ddA into ddI would be 99%; see Table 2, page 1502. They also teach that the product should be "virtually 100% pure on the basis of the HPLC analyses", page 1503, description of Fig. 1. Thus, on having ordinary skills in the art would obtain under applied conditions of synthesis and purification ddI product with at least 96% yield and about 99% pure. In conclusion, the invention of claim 21 was within the ordinary skill in the art to make and use at the time it was made, and was as a whole, *prima facie* obvious.

Conclusion

All claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka whose telephone number is (571) 272-0944. The examiner can normally be reached on Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Malgorzata A. Walicka, Ph.D.

Art Unit 1652

Patent Examiner

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